Pergamon

Tetrahedron Letters 39 (1998) 1877–1880

TETRAHEDRON LETTERS

A Novel Monoalkylation of Symmetrical α-Diones

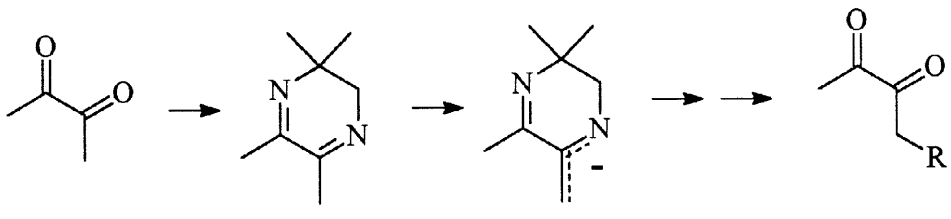
Damodaragounder Gopal,[1] Durgesh V. Nadkarni,[2] and Lawrence M.Sayre*
Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Received 20 October 1997; accepted 19 November 1997

Abstract: An efficient method has been developed for the synthesis of monoalkylated 1,2-diones by using steric approach control. The dihydropyrazine **2** prepared from 2,3-butanedione and 1,2-diamino-2-methylpropane is selectively deprotonated on the less hindered methyl group to give an anion which is alkylated with alkyl iodides and activated bromides. *In situ* hydrolysis of the alkylated dihydropyrazines gives monoalkylated diones **4** in good yield.

In our studies related to the preparation of aminodiones, we were interested in the possibility of monoalkylating symmetrical α-diketones such as 2,3-butanedione. By themselves, α-diketones are important intermediates in the synthesis of pyrazines[1,2] used as flavorants[3] and other natural products.[4,5] The current general methods for synthesis of unsymmetrical α-diketones involve the oxidation of the corresponding alkynes by ruthenium tetroxide,[6] neutral potassium permanganate,[7] selenium dioxide with sulfuric acid,[8] N-bromosuccinimide/dimethyl sulfoxide,[9] and thallium(III) nitrate,[10] as well as the selenium dioxide oxidation of ketones.[11] Alternatively, α-diketones can be extended by converting them into the corresponding diimines, followed by deprotonation with LDA, alkylation, and hydrolysis.[12] However this alkylation method is not suitable for the monoalkylation of symmetrical α-diketones like 2,3-butanedione as it produces a mixture of mono and dialkylated products along with unalkylated starting material.[12] We attempted to alkylate 2,3-butanedione directly by converting it into either the corresponding monoanion or dianion (by one or two equivalents of LDA), but this failed to furnish any desired products.

The new approach we considered was based on the expected selective monodeprotonation of the dihydropyrazine intermediate **2** by LDA on account of steric inhibition of solvation of the lithium anion derived from the *tert*-alkyl imine. The resulting anion **3** was expected, upon alkylation followed by hydrolysis, to give monoalkylated diones **4** as shown in Scheme 1.



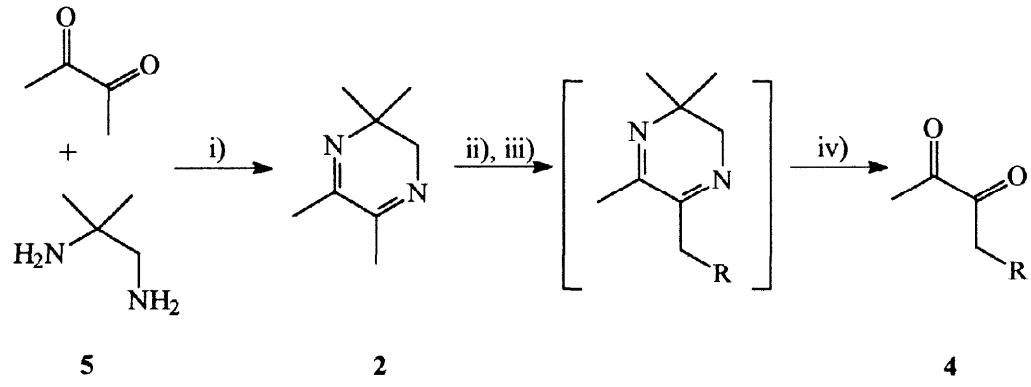
1 **2** **3** **4**

Scheme 1

a. Current address: Research Organics, Inc., Cleveland OH
b. Current address: Occidental Chemical Co., Ashtabula OH

0040-4039/98/$19.00
PII: S0040-4039(98)00306-2

The condensation of 2,3-butanedione and 1,2-diamino-2-methylpropane (**5**) in the presence of *p*-toluenesulfonic acid provided the required 2,2,5,6-tetramethyl-2,3-dihydropyrazine (**2**) in 68 % yield. Dihydropyrazine **2** was selectively deprotonated on the less hindered methyl group using one equivalent of LDA in THF at -78 °C. The monoanion was alkylated with benzyl bromide at temperatures below -50 °C followed by *in situ* hydrolysis by the addition of hydrochloric acid. The workup of the reaction gave an 84% yield of 5-phenylpentane-2,3-dione (**4a**). The general applicability of the method is illustrated in Table 1. The reaction is quite successful for activated and unactivated alkyl iodides and activated bromides (allyl and benzyl). However the reaction failed to give any identifiable products for chlorides and unactivated bromides.



5 **2** **4**

i) *p*-toluenesulfonic acid, ii) 1 eq. LDA, iii) alkyl halide, iv) 1 N HCl

The limiting factor of this novel method is the instability of the monoanion at temperatures above -50 °C. Above this temperature (when stored for more than one hour) the reaction resulted in unidentifiable products even for the iodides and activated bromides. In this connection, it is also interesting to note that the dihydropyrazine **2** itself when stored for more than a week at -15 °C dimerized to a crystalline solid.[13,14]

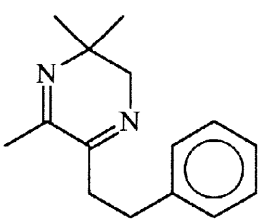
The observation that the reaction gives good yields of the monoalkylated products supports our prediction of the selective deprotonation of dihydropyrazine **2**. However this does not prove the achievement of selective deprotonation at the 5-methyl group of **2**. In this connection we decided to characterize the regiochemistry of alkylated dihydropyrazine **6**. Due to its expected low stability, compound **6** was isolated by rapid evaporation of the solvent at reduced pressure and analyzed by ^{1}H NMR spectrometry without purification. The structural assignment was anticipated on the basis of the fact that the C3 methylene group in dihydropyrazine **2** (3.33 δ, 2H quartet, J = 1.8 Hz) exhibits long range coupling to the 5-methyl group (2.13 δ, 3H triplet, J = 1.8 Hz). The 6-methyl group, on the other hand, is a 3H singlet (2.09 δ). The C3 methylene for the benzylated dihydropyrazine appeared as a 2H triplet (at 3.31 δ, J = 1.9 Hz) rather than as a quartet, and the remaining 3H methyl signal was a singlet (at 2.03 δ). This clearly confirms that the benzylated dihydropyrazine

Table 1. Preparation of α–Diketones from 2,2,5,6-Tetramethyl-2,3-dihydropyrazine (**2**)

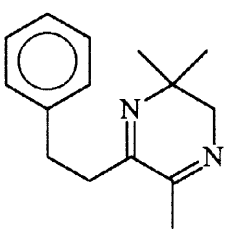
No.	Alkyl group	Halide	Product	Yield (%)
1	Benzyl	Bromide	**4a**	84
2	Benzyl	Chloride	**4a**	-[a]
3	Allyl	Bromide	**4b**	34[b]
4	Allyl	Iodide	**4b**	35[b]
5	Crotyl	Bromide	**4c**[c]	47[b]
6	Cyclohexenyl	Bromide	**4e**	62
7	1-Butyl	Iodide[d]	**4d**	60
8	Phenethyl	Iodide[d]	**4f**	76

a. No characterizable products were isolated.
b. The lower yields are probably due to the poor extraction of the products.
c. Isomeric mixtures.
d. The corresponding bromide was insufficiently reactive.

is **6** and not **7** (the 5-methylene 2H signal appeared as a multiplet at 2.8 - 2.9 δ), demonstrating that the alkylation proceeds regiospecifically as shown in Scheme 1.



6



7

General procedure. To a solution of the dihydropyrazine **2**[15] (0.01 mol) in 75 mL of THF maintained at -78° C is added one equivalent of LDA. The solution is stirred for five minutes followed by addition of alkyl halide (0.02 mol). The temperature of the reaction mixture is gradually allowed to come to -50 °C during a period of one hour, 75 mL of 1 N HCl was added, and the cooling bath was removed. After one hour of stirring, the THF was removed by rotary evaporation, and the remaining aqueous layer was extracted with dichloromethane. The organic extract was washed with 1N HCl, water, and saturated sodium bicarbonate

solution, and then dried (Na_2SO_4). Concentration of the dichloromethane solution gave a mixture of alkyl halide and the product, which was purified by silica gel chromatography (dichloromethane) to yield diketones **4**, which were characterized by ^1H NMR spectrometry. For the more volatile products 4b-4d, a different workup was used, whereby following only partial removal of THF, the aqueous THF layer was diluted with diethyl ether, the organic layer was separated, washed and dried as above, and the diethyl ether was removed by rotary evaporation at low temperature prior to chromatography of the residue.

In conclusion we have developed a mild method which is valuable for the synthesis of unsymmetrical α-diketones, even containing functional groups such as double bonds which are susceptible to oxidation by reagents which are used in the most common acetylene-based α-diketone syntheses.

Acknowledgment. This work was supported by grants NS 22688 and GM 48812 from the National Institutes of Health.

References and notes:

1. Felder, E.; Pitre, D.; Boveri, S.; Grabitz, E. *Chem. Ber.* **1967**, *100*, 555-559.
2. Flament, I.; Stoll, M. *Helv. Chim. Acta* **1967**, *50*, 1754-1758.
3. Akiyama, T.; Enomoto, Y.; Shibamoto, T. *J. Agric. Food Chem.* **1978**, *26*, 1176-1179.
4. Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3460-3467.
5. Kelly, T. R.; Chandrakumar, N. S.; Cutting, J. D.; Goehring, R. R.; Weibel, F. R. *Tetrahedron Lett.* **1985**, *26*, 2173-2176.
6. Gopal, H; Gordon, A. J. *Tetrahedron Lett.* **1971**, 2941-2944.
7. Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1979**, *44*, 2726-2730.
8. Sonoda, N.; Yamamoto, Y.; Murai, S.; Tsutsumi, S. *Chem. Lett.* **1972**, 229-232.
9. Wolfe, S.; Pilgrim, W. R.; Garrard, T. F.; Chamberlain, P. *Can. J. Chem.* **1971**, *49*, 1099-1105.
10. McKillop, A.; Oldenziel, H.; Swann, B. P.; Taylor, E. C.; Robey, R. L. *J. Am. Chem. Soc.* **1973**, *95*, 1296-1301.
11. Rabjohn, N. *Org. Reactions* **1976**, *24*, 261-415.
12. De Kimbe, N.; Dhondt, L.; Stanoeva, E. *Tetrahedron Lett.* **1991**, *32*, 3879-3882.
13. Gopal, D.; Macikenas, D.; Sayre, L. M.; Protasiewicz, J. D. *Acta Chem. Scand.* **1997**, *51*, 938-941.
14. Yamaguchi, T.; Eto, M.; Watanabe, K.; Kashige, N.; Harano, K. *Chem. Pharm. Bull.* **1996**, *44*, 1977-1979.
15. 2,2,5,6-Tetramethyl-2,3-dihydropyrazine (**2**) was prepared from equimolar amounts of 2,3-butanedione and 1,2-diamino-2-methylpropane (**5**) by azeotropic removal of the water formed using a Dean-Stark apparatus (benzene reflux, in the presence of 1 mol % *p*-toluenesulfonic acid). The reaction is stopped as soon as the required amount of water is collected, and the residue obtained upon evaporation of solvent is immediately distilled. The desired product has b.p. 50 °C at 10 mm Hg; yield 68%.